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UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

ARIA DIAGNOSTICS, INC. Plaintiff, v. SEQUENOM, INC., Defendant/ Counterclaim-Plaintiff, v. ARIA DIAGNOSTICS, INC., Counterclaim-Defendant, and ISIS INNOVATION LIMITED, Nominal Counterclaim-Defendant.	Case No. 3:11-cv-06391-SI **REPLY IN SUPPORT OF SEQUENOM'S MOTION FOR PRELIMINARY INJUNCTION** Date: June 22, 2012 Time: 9:00 AM Place: Courtroom 10, 19th Floor Judge: Hon. Susan Illston

TABLE OF CONTENTS

Page

I. ARIOSA INFRINGES 1
A. Sequenom Will Likely Prove That The Harmony Prenatal Test Infringes 1
1. Ariosa "Amplifies" 3
2. Ariosa Detects "Paternally Inherited Nucleic Acid" 4
3. Ariosa's Proposed Construction Is Unsupported 6
II. ARIOSA FAILED TO PRODUCE PERSUASIVE EVIDENCE OF INVALIDITY 7
A. The '540 Patent Is Directed to Patentable Subject Matter 7
1. The '540 Patent Claims Do Not Preempt All Use Of A Natural Law 7
2. The Claims Of The '540 Patent Do Not Preempt Future Innovation 8
3. The Claim Elements Are Not "Merely Conventional" 8
B. Ariosa Mistakenly Examines Its Own Product For Enablement 9
C. Ariosa Fails To Raise A Substantial Question As To the Validity Of The '540 Patent Based On The Kazakov Reference 10
III. SEQUENOM HAS DEMONSTRATED IRREPARABLE HARM 11
A. The Ariosa-LabCorp Deal Exponentially Increases The Likelihood That Sequenom Will Suffer Loss Of Market Share, Goodwill And Reputation 12
B. Ariosa's Opposition Confirms The Likelihood Of Price Erosion 14
C. Harm Sequenom's Ability To Raise Capital; Ariosa's Inability To Pay Damages 15
IV. THE BALANCE OF HARDSHIP AND PUBLIC INTEREST FACTORS 15

TABLE OF AUTHORITIES

Page

Cases

Amgen Inc. v. Hoechst Marion Roussel, Inc.,
314 F.3d 1313 (Fed. Cir. 2003) 10

Aventis Pharma S.A. v. Hospira, Inc.,
675 F.3d 1324 (Fed. Cir. Apr. 9, 2012) 6

Bettcher Indus., Inc. v. Bunzl USA, Inc.,
661 F.3d 629 (Fed. Cir. 2011) 10

CFMT, Inc. v. Yieldup Int'l. Corp.,
349 F.3d 1333 (Fed. Cir. 2003) 10

Connell v. Sears, Roebuck & Co.,
722 F.2d 1542 (Fed. Cir. 1983) 9

Continental Can Co. v. Monsanto Co.,
948 F.2d 1264 (Fed. Cir. 1991) 11

Data Quill Ltd. v. Handspring, Inc.,
2003 WL 737785 (N.D. III., Feb. 28, 2003). 2

Diamond v. Diehr,
450 U.S. 175 (1981) 7, 9

Glaxo Inc. v. Novo-pharm Ltd.,
52 F.3d 1043 (Fed. Cir. 1995) 11

Inline Connection Corp. v. Earthlink, Inc.,
684 F. Supp.2d 496 (D. Del. 2010) 10

Invitrogen Corp. v. Clontech Labs., Inc.,
429 F.3d 1052 (Fed. Cir. 2005) 7, 10

Mayo Collaborative Servs. v. Prometheus Labs. Inc.,
132 S.Ct. 1289 (2012) ..... iv, 7, 8, 9

MBO Labs., Inc. v. Becton, Dickinson & Co.,
474 F.3d 1323 (Fed. Cir. 2007) 2

Momenta Pharms., Inc. v. Amphastar Pharms., Inc.,
2011 WL 5882184 (D. Mass. Nov. 23, 2011) 12

Nazomi Commc'ns, Inc. v. Samsung Telecomms., Inc.,
2012 WL 967968 (N.D. Cal. Mar. 21, 2012) 8

PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,
491 F.3d 1342 (Fed. Cir. 2007) 2

Robert Bosch LLC v. Pylon Mfg. Corp,
659 F.3d 1135 (Fed Cir. 2006) 14

Sanofi-Synthelabo v. Apotex, Inc.,
470 F.3d 1368 (Fed. Cir. 2006) 15

Titan Tire v. Case New England Holland, Inc.,
566 F.3d 1372 (Fed. Cir. 2009) 7

TruePosition Inc. v. Andrew Corp.,
568 F.Supp.2d 500 (D. Del. 2008) 14

Verizon Serv's Corp. v. Vonage Holdings Corp.,
503 F.3d 1295 (Fed. Cir. 2007) 4

Vulcan Engineering Co., Inc. v. FATA Aluminum, Inc.,
278 F.3d 1366 (Fed. Cir. 2002) 10

ZMI Corp. v. Cardiac Resuscitator Corp.,
844 F.2d 1576 (Fed. Cir. 1988) 4

Statutes

35 U.S.C. § 101 ..... 7, 8, 9

Other Authorities

Wright & Miller:
Federal Prac. & Proc. s 2948.1 11

NOTES ON CITATIONS

The following citation conventions are used in this brief:

- '540 patent or '540 = the patent-in-suit, U.S. Patent No. 6,258,540.
- Sequenom = Sequenom, Inc.
- Ariosa = Ariosa Diagnostics, Inc.
- cffDNA = cell-free fetal nucleic acid
- *Prometheus* = *Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 132 S.Ct. 1289 (2012)
- Mot. = Sequenom, Inc.'s Motion for Preliminary Injunction
- Opp. = Ariosa Diagnostics, Inc.'s Opposition To Sequenom, Inc.'s Motion for Preliminary Injunction
- Root Decl. = Declaration of Peter Root filed concurrently with Sequenom, Inc.'s Reply in Support of Sequenom's Motion for Preliminary Injunction
- Evans Suppl. Decl. = Supplemental Declaration of Dr. Mark I. Evans filed concurrently with Sequenom, Inc.'s Reply in Support of Sequenom's Motion for Preliminary Injunction
- Welch Suppl. Decl. = Supplemental Declaration of William Welch filed concurrently with Sequenom, Inc.'s Reply in Support of Sequenom's Motion for Preliminary Injunction
- Evans Decl. = Declaration of Dr. Mark I. Evans in Support of Sequenom's Motion for Preliminary Injunction (Docket Number 35)
- Welch Decl. = Declaration of William Welch in Support of Sequenom's Motion for Preliminary Injunction (Docket Number 36)
- Rao Decl. = Declaration of Dr. Mohan Rao in Support of Sequenom's Motion for Preliminary Injunction (Docket Number 38)
- Bisc. Decl. = Declaration of Dr. Farideh Bischoff in Support of Ariosa's Opposition (Docket Number 83)
- Fear. Decl. = Declaration of Dr. Eric R. Fearon in Support of Ariosa's Opposition (Docket Number 84)
- Steul. Decl. = Declaration of Dr. John Steulpnagel in Support of Ariosa's Opposition (Docket Number 97)
- Sull. Decl. = Declaration of Dr. Ryan Sullivan in Support of Ariosa's Opposition (Docket Number 98)

The Court has every reason to grant a preliminary injunction in this case. Sequenom spent many years and tens of millions of dollars developing and bringing to market a revolutionary non-invasive prenatal test for Down syndrome and other fetal aneuploidies on the promise that its investment and pioneering efforts would be protected by its patent rights. Ariosa is trampling Sequenom's patent rights and threatening to destroy Sequenom's rightful leadership position in this brand new market in ways that can never be compensated with money damages. No more is needed to justify enjoining Ariosa's infringing activity. But there is more. Ariosa's callous indifference to Sequenom's patent rights is matched by Ariosa's callous indifference to pregnant women: Ariosa is marketing its infringing test to all pregnant women, including those at low-risk for fetal aneuploidies, despite that its test has not been clinically validated for use in the low-risk population. Ariosa is ignoring FDA guidance on the need to validate before marketing. It is ignoring the National Society of Genetic Counselors, whose considered policy is that these tests should be used only in the high-risk population for which they have been validated. Ariosa's indiscriminate, saturation bombing of this new market with its infringing test threatens irreparable harm to Sequenom, unsuspecting pregnant women, and the market itself. In this case, injunctive relief is more than justified—it is imperative.

I. ARIOSA INFRINGES

A. Sequenom Will Likely Prove That The Harmony Prenatal Test Infringes

Ariosa infringes. It concedes all the factual elements: obtaining a non-cellular fraction of a maternal blood sample, amplifying a paternally inherited nucleic acid from the non-cellular fraction, and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid. In a futile attempt to avoid the inevitable conclusion of infringement, Ariosa seeks claim constructions designed to obscure these clear facts. Its proposed claim constructions, however, are convoluted and implausible, and should be rejected.

Ariosa's Harmony test specifically uses a "polymorphic assay" to find the fraction of fetal DNA in the maternal plasma sample. The "fetal fraction" is critical to accuracy of the Harmony test. Root Decl. Ex. 1 at 243:15-23. To determine the fetal fraction, the polymorphic assay intentionally and specifically looks for small numbers of paternally inherited sequences. Ariosa admits that "[b]y examining chromosomal loci where different sequences are expected to occur in the mother and fetus,

the polymorphic assay determines the percentage of fetal nucleic acids and the percentage of maternal nucleic acids in the sample." Opp. at 15. Ariosa expects "different sequences . . . to occur" precisely because the father will contribute a different sequence, *i.e.*, the different sequence found in the fetal DNA is paternally inherited. Evans Suppl. Decl. ¶¶ 71-77. Simply put, the polymorphic assay is specifically designed to detect fetal nucleic acids uniquely inherited from the father, after amplification of DNA from a maternal plasma sample.

Ariosa's own publication notes that its selection of polymorphic loci was "optimized for minor allele frequency," which means that it *expected* to be able to distinguish between maternal and paternal DNA at those loci. Evans Decl. Ex. 6 at pg. 6; Evans Suppl. Decl. ¶ 71. Further, though Ariosa studiously avoids using the term, a study its publication cites to as using polymorphic loci expressly notes that the method detects "***paternally inherited*** polymorphic biallelic markers." Evans Suppl. Decl. ¶ 72. In short, infringement is not a close call.

Finding itself without noninfringement facts, Ariosa tries to concoct claim constructions to manufacture a noninfringement argument, but produces a confused and sometimes meaningless mess. Its proposed constructions are not the ordinary meanings, are not drawn from the patent (and in fact, exclude the examples given in the patent), and produce absurd results. The Court should reject Ariosa's claim construction-dependent noninfringement argument.[1] *See MBO Labs., Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1333 (Fed. Cir. 2007) (noting that "[a] claim interpretation that excludes a preferred embodiment from the scope of the claim is rarely, if ever, correct") (citation omitted); *see also Data Quill Ltd. v. Handspring, Inc.*, 2003 WL 737785, at * 4 (N.D. III., Feb. 28, 2003) (striking an expert's report and declaration as unreliable in part because the expert failed to follow the proper infringement analysis of applying properly construed claims). Moreover, even if Ariosa's claim constructions are accepted in part, the record clearly shows that Ariosa infringes.

[1] In addition to ignoring well-settled law on claim construction, Ariosa's expert fundamentally misapprehended the infringement analysis. At deposition, Dr. Bischoff admitted that she compared Ariosa's Harmony test to Sequenom's MateriT21, rather than solely comparing the Harmony test to '540's claims as required. Root Decl. Ex. 3 at 142:20-25; 150:25-151:3. As a result, the Court should disregard all of Dr. Bischoff's opinions on infringement. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1354-55 (Fed. Cir. 2007) (affirming striking expert testimony on infringement when based on unreasonable interpretation).

1. Ariosa "Amplifies"

The evidence demonstrates that the Harmony test "amplifies" paternally inherited nucleic acids under either Sequenom's correct construction or Ariosa's incorrect, strained construction. Ariosa's Chief Scientific Officer, Dr. Oliphant, admitted that Ariosa amplifies cffDNA from maternal plasma: "In the DANSR process we isolate cell-free DNA from the maternal blood. We hybridize oligonucleotides to that cell-free DNA. We ligate those oligonucleotides together, ***amplify*** those oligonucleotides, and then sequence those products."[2] Root Decl. Ex. 2 at 31:18-22, 41:23-43:5.

Sequenom's construction of amplifying—"increasing the amount by making copies"—is entirely consistent with and supported by '540's claims, specification and file history, and how Ariosa's own experts understand the term. Dr. Bischoff testified that "[a]mplification can be a form of making multiple copies of sequences." Root Decl. Ex. 3 at 35:16-20. Numerous biochemical and medical dictionary definitions define "amplify" as simply increasing in amount, with no requirement for "increasing the relative concentration" as Ariosa contends. Root Decl. Exs. 4-5. Even Dr. Bischoff, in one of her own patent applications in the prenatal analysis field, defined amplification as "increasing the number of DNA molecules having a specific sequence." Root Decl. Ex. 6. Likewise, Dr. Fearon admitted that "[t]he polymerase chain reaction is a way of increasing the abundance of specific DNA sequences." Root Decl. Ex. 7 at 134:3-5. It is undisputed that Ariosa infringes under this definition. Evans Decl. ¶¶ 98-103.

Ariosa's construction, "'increasing the relative concentration of'" (Opp. at 16:27-28), ignores the plain reading of the claims and the specification. *Id*. Ariosa seizes on the word "enrichment" in the '540 specification. Opp. at 16. But the claim term is "amplifying," not enrichment. Those words mean different things in the '540 patent: Claim 19 requires both the presence of amplification and the absence of an enrichment step; thus, amplification is not the same as enrichment as used in the '540.

The Harmony test also infringes even under Ariosa's own strained "'increasing the relative concentration of'" construction. Opp. at 16:27-28. The Harmony test amplifies all the nucleic acids at

[2] The Harmony test uses polymerase chain reaction ("PCR") a well-established method for increasing the amount of nucleic acids by making copies of them, *i.e.*, amplifying them. Root Decl. Ex. 2 at 42:8-20 & Ex. 3 at 36:3-10, 123:16-21.

the selected 192 polymorphic loci and 576 nonpolymorphic loci, and leaves unamplified all remaining nucleic acids in the sample, thus increasing the relative concentration of the selected loci. Root Decl. Ex. 2 at 221:24-222:6 & Ex. 8 at pg. 5-6. Thus, Ariosa infringes under either construction.

2. Ariosa Detects "Paternally Inherited Nucleic Acid"

Ariosa proffers no noninfringement theory under Sequenom's proposed construction of "paternally inherited nucleic acid" ("a nucleic acid that originates from the fetus and is inherited from the father"), but the Harmony test also infringes even if the term is construed to require a "known sequence received only from the father."[3] Ariosa's construction is more convoluted: (i) a known sequence received only from the father and (ii) ***not*** fetal sequence which differs from that of the mother. Opp. at 7:14-16. That results in a null set—there can be no sequence received ***only*** from the father ***and*** which does not differ from that of the mother—an absurd result. *See ZMI Corp. v. Cardiac Resuscitator Corp.*, 844 F.2d 1576, 1578 (Fed. Cir. 1988) (noting that "an improper determination of the scope of the claims, can distort the entire infringement analysis").

Further, Ariosa admits that Y chromosome sequences are "absent from a woman's genome." Opp. at 8:23-24. In other words, a fetal Y chromosome sequence is a "fetal sequence which differs from that of the mother." But under Ariosa's construction ("not fetal sequence which differs from that of the mother") detecting a Y chromosome sequence would not be covered by any of the claims of the '540 patent. The same is true for another example from the specification—the RhD gene, which can be absent from the mother's genome but detected if present in the fetus' genome when inherited from the father. *See Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1305 (Fed. Cir. 2007) (rejecting Vonage's proposed construction because its reading "would exclude several examples in the specification . . . .").

Ariosa is also just wrong on the facts: as Dr. Oliphant admitted, for each of the 192 loci selected as part of the polymorphic assay, the sequences ***are*** known in advance, and the Harmony test

[3] Due to space constraints, for purposes of this reply, Sequenom focuses only on the parts of the Harmony test that clearly infringe even requiring a "known sequence received only from the father." Sequenom reserves the right to maintain additional infringement theories under its proposed constructions.

in fact counts the alleles by comparing their sequences to ***known*** sequences of the "A" allele and the "B" allele at that locus. Root Decl. Ex. 2 at 187:3-25. Ariosa's polymorphic assay looks to see if the father has contributed to the fetus a sequence different from that contributed by the mother so that difference can be used to quantify the fetal fraction. This is just like looking for a Y chromosome sequence or Rhesus D sequence that will only be present if the father contributed it to the fetus—the very examples given in the '540 patent.

DNA sequences are highly conserved (almost identical) among humans. Evans Suppl. Decl. ¶ 73. One type of genetic variance is the single nucleotide polymorphism ("SNP"), which means a change to only a single base in a sequence. *Id.* At any particular location ("locus") in the genome, a variant sequence is called an allele. *Id.* SNPs can have four variants (A, C, G, or T), but for its assay, Ariosa selects "biallelic" loci, where there are typically only two allele variants. *Id.*; Root Decl. Ex. 2 at 35:22-36:10. The allele that appears less frequently in the population is called the "minor allele," and Ariosa targets alleles with "high minor allele frequencies" because the higher the minor allele frequency, the more likely any given SNP will be informative because the fetus is more likely to have inherited a different allele from each of the mother and father. Root Decl. Ex. 2 at 35:22-36:10; Evans Suppl. Decl. ¶ 73. When Ariosa detects an allelic imbalance at one of the polymorphic loci, Ariosa is necessarily detecting a paternally inherited nucleic acid from the fetus. Evans Suppl. Decl. ¶ 73.

Again, ***Ariosa knows those sequences in advance***: "To assess fetal fraction, we designed assays against a set of 192 SNP- containing loci on chr 1-12, where two middle oligos, differing by one base, were used to query each SNP," *i.e.*, the oligos are sequence-specific to one of two known alleles. Thus, even interpreting the claims to require a "known sequence received only from the father," Ariosa infringes.[4]

One does not know in advance whether the Y chromosome sequence will be present. One does not know in advance whether the Rhesus D sequence will be present in a Rhesus D negative

[4] Ariosa has hinted at the possibility that there could be other sources of allelic imbalance in its assay, but in the overwhelming majority of cases, the imbalance is due to the detection of paternally inherited nucleic acid. Spontaneous mutations are much too rare to make up any appreciable portion of the detected nucleic acid in Ariosa's test. Evans Suppl. Decl. ¶¶ 76-77.

mother. But if one detects those sequences, one concludes that they came from the father because one knows that the mother did not contribute the Y or Rhesus D sequences. In the same way, in the polymorphic assay, a signal count showing an allelic imbalance means that sequence A came from mom and sequence B came from the fetus via paternal inheritance.

3. Ariosa's Proposed Construction Is Unsupported

"Known sequence received only from the father," moreover, is an improper construction, which Ariosa reads in by interpreting certain examples in the specification. Opp. at 8:27-9:1. But claims are not to be limited to the examples in a patent. *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1331 (Fed. Cir. 2012) (general descriptions or examples "do not suffice to limit the claims"). Ariosa also purports to rely upon the '540 prosecution file history to limit the meaning of "paternally inherited nucleic acid" to "a known sequence received only from the father." Opp. at 9:22-11:3. But nowhere in the prosecution history did the examiner require, nor did the applicants agree, that "paternally inherited" should be limited to a sequence known in advance.

Ariosa's only alleged justification for its "not fetal sequence which differs from that of the mother" construction comes from the continuation application file history, not the '540 patent file history. Opp. at 11, citing Bisc. Decl. at ¶¶ 59-67. During prosecution of the continuation application, the applicants stated that:

> the term 'paternally inherited' does not cover the cases: (a) in which a gene is **maternally inherited**, yet the nucleic acid is not (in total) the same in the fetus as in the mother, and (b) in which the gene is **altered spontaneously**, for example, in the egg or sperm, i.e., by what appears to be chance or sporadic mutation.

Bisc. Decl. at ¶ 60 & Bisc. Decl. Ex. 27 (emphasis added).

This simply does not say that "paternally inherited" means "a known sequence received only from the father, and not fetal sequence which differs from that of the mother." And when the examiner of the continuation application argued that "[the] description does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome," she was not referring to any claims that included the limitation "paternally inherited." Bisc. Decl. at ¶ 64 & Ex. 31. At the time that the continuation application was abandoned (with no agreement reached between the applicant and the examiner) there were no pending claims with the words "paternally inherited." Bisc. Decl. Exs. 37

& 48. Thus, the abandonment has no bearing whatsoever on the meaning of "paternally inherited" in the already issued claims of the '540 patent. *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1078 (Fed. Cir. 2005) (related patent applications cannot disclaim claim scope in the other application when the claim language is different).

II. ARIOSA FAILED TO PRODUCE PERSUASIVE EVIDENCE OF INVALIDITY

"[W]hen analyzing the likelihood of success factor, the trial court, after considering all the evidence available at this early stage of the litigation, must determine whether it is more likely than not that the challenger will be able to prove at trial, by clear and convincing evidence, that the patent is invalid." *Titan Tire Corp. v. Case New England Holland, Inc.*, 566 F.3d 1372, 1379 (Fed. Cir. 2009). Ariosa has not presented any meaningful challenge to the validity of the '540 patent.

A. The '540 Patent Is Directed To Patentable Subject Matter

1. The '540 Patent Claims Do Not Preempt All Use Of A Natural Law

Ariosa wrongly asserts that the claims of '540 capture a "law of nature." The '540 claims do not cover the *existence* of natural relationships (*e.g.* between metabolite concentrations and drug efficacy), equations describing a law of nature (*e.g.* $E = mc^2$), or a natural phenomenon (*e.g.* the *existence* of cffDNA in maternal blood). *Cf. Prometheus*. Rather, the '540 claims are directed to particular ways of manipulating the cffDNA present in maternal blood. *See id.* at 1299, *citing Diamond v. Diehr*, 450 U.S. 175, 187 (1981) (inventions which include a "law of nature" are patent eligible if the claims "transformed the process into an inventive application . . . .").

Of course, "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Prometheus* at 1293. Therefore, "too broad an interpretation of this exclusionary principle [§101] could eviscerate patent law." *Id*. The '540's claims of course *make use* of the fact that there is cffDNA in maternal blood, but do not preempt all use of that phenomenon. The claims require the particular steps of (1) separating the serum or plasma from the blood (not a natural phenomena nor required to use cffDNA), (2) amplifying the nucleic acid (not a natural phenomena nor required to use cffDNA), and (3) detecting paternally inherited nucleic acid (not a natural phenomena). *See Diehr*, 450 U.S. at 187 ("[T]hey seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process."). The '540 does not

merely recite a natural law and say "apply it" (*Prometheus* at 1294); rather, the claims "recite specific steps that confine the claims to a specific, useful application." *Nazomi Commc'ns, Inc. v. Samsung Telecomms., Inc.*, 2012 WL 967968, *4 (N.D. Cal. Mar. 21, 2012) (claims eligible under § 101 because directed to specific steps and did not preempt the use of an abstract idea (*citing Prometheus* at 1293-1302)).

2. The Claims Of the '540 Patent Do Not Preempt Future Innovation

The '540 claims do not "disproportionately t[ie] up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *Prometheus* at 1294. Ariosa's dire warnings that '540 preempts all "clinically useful developments" (Fear. Decl. at ¶121) are baseless because there are other ways to use cffDNA in maternal blood.

The '540 claims require amplification of the paternally-inherited fetal nucleic acid. Methods ***that do not involve the transformative step of amplification*** are not preempted. The single-molecule sequencing technology is one such example. Root Decl. Ex. 7 at 90:3-91:10 (single-molecule sequencers do not require amplified nucleic acids). Further, the use of the single-molecule, non-amplification method for the non-invasive detection of trisomy from cffDNA was recently published in a peer-reviewed journal. Evans Suppl. Decl. ¶ 26. The '540 claims also require removing the cellular component of the blood, leaving plasma or serum. Methods ***that do not require the transformative step of fractionation*** are not preempted. Researchers, including Ariosa's own expert, Dr. Bischoff, have detected cffDNA from whole maternal blood without removing the cellular component. Root Decl. Ex. 3 at 107:3-108:12, 178:2-179:21 & Root Decl. Ex. 10; Evans Suppl. Decl. ¶ 27 . The availability of such methods allows use of the underlying "natural phenomenon" in other inventions. *See Prometheus* at 1301.

3. The Claim Elements Are Not "Merely Conventional"

Ariosa's argument that the steps in the claimed methods consist merely of "'well-understood, routine, conventional activity already engaged in by the scientific community'" completely misrepresents how those steps were in fact used in the field of prenatal diagnosis. Opp. at 6:27-7:2. The ability to detect cffDNA, rather than intact fetal cells, in maternal plasma through a fractionation/

amplification/detection assay was not known ***at all***. Evans Decl. ¶¶ 39-40, 70-73.[5] That this was unknown is exemplified by the fact that, previously, researchers actually discarded the non-cellular fraction of maternal blood. *Id*. The scientific community and the PTO recognized the claims of the '540 patent, including the use of fractionation, amplification, and detection, as surprising, inventive, and groundbreaking. *Id*. ¶¶ 45-47, 70-73; Evans Suppl. Decl. Exs. 20-23; Root Decl. Exs. 10-11.

The present challenge stands in stark contrast to the situation in *Prometheus*, where the basic correlation between metabolite levels and dosage was already known. *Prometheus* at 1295. And as *Prometheus* noted, "'[a] new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made.'" *Id.* at 1298, *citing Diehr*, 450 U.S. at 188. There is no requirement in patent law that ideas spring into being *ex nihilo*:

> This is particularly true in a process claim because a new combination of steps in a process may be patentable **even though all the constituents of the combination were well known and in common use before the combination was made.** The "novelty" of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter.

Diehr at 188-89; *see also Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1549 (Fed. Cir. 1983) (it cannot be the law "that an invention meeting with great skepticism and great acclaim would be unpatentable 'if the elements comprising the invention are disclosed by an examination of the prior art.'").

B. Ariosa Mistakenly Examines Its Own Product For Enablement

Ariosa agrees that the '540 claims are enabled to do what they describe—detect paternally inherited nucleic acids. Opp. at 8:18-19. This admission defeats the enablement attack. Ariosa argues that its Harmony test was not enabled by the specification. Opp. at 18:9-10. But enablement does not turn on whether the accused product is enabled. *Inline Connection Corp. v. Earthlink, Inc.*, 684 F.

[5] Indeed, Ariosa's expert who opined on § 101 issues, Dr. Fearon, is not an expert in prenatal diagnosis, and in the 1990s, was unaware of Dr. Lo's groundbreaking work. Root Decl. Ex. 7 at 19:18-25 (stating he did not have an understanding of Dr. Lo's research program in 1997). Ariosa's other expert witness, Dr. Bischoff, only used cffDNA in her work after Dr. Lo's widely reported work. Root Decl. Ex. 3 at 179:25-180:19 & Exs. 10-12.

Supp. 2d 496, 526-27 (D. Del. 2010) (an argument "that the patents-in-suit must enable the accused product" is "flatly contrary to a proper enablement analysis"). All that is required is that the specification enables some mode of practicing the invention. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1335 (Fed. Cir. 2003) (irrelevant that the patent did not disclose a later-developed method used by infringer). The enablement inquiry properly examines whether one skilled in the art could have practiced the steps set forth in the claims in 1997, not whether one skilled in the art could have detected Down's syndrome using cffDNA in 1997. *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1071(Fed. Cir. 2005). Because the asserted claims are "comprising" claims, the Harmony test infringes if it practices all of the claim limitations, even if it also involves other steps. *Vulcan Eng'g. Co., Inc. v. FATA Aluminum, Inc.*, 278 F.3d 1366, 1375-1376 (Fed. Cir. 2002) ("when all of the claimed features are present in the accused system, the use of additional features does not avoid infringement"). Ariosa's test infringes because it uses the '540's claimed methods, period.

Further, scientists used the claimed methods to detect Down's syndrome, although the methods may not have been commercially viable. Evans Suppl. Decl. ¶ 33. "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l. Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003).

C. Ariosa Fails To Raise A Substantial Question As To The Validity Of The '540 Patent Based On The Kazakov Reference

Six months after filing a declaratory judgment action without an allegation of invalidity and four months after the preliminary injunction motion was filed, Ariosa has still failed to identify a piece of prior art that it alleges expressly anticipates the '540. The best it can muster is to say that a reference (Kazakov) cited in the patent file history might theoretically "inherently anticipate," *i.e.*, Ariosa concedes that the reference does not expressly contain all of the elements of the asserted claims. Thus, its inherency argument depends on the proposition that the claimed steps ***necessarily*** and ***inevitably*** resulted from the practice of the prior art reference. *See Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (en banc) ("Inherency . . . may not be established by probabilities or possibilities").

Ariosa's own expert cannot support the inherency theory. Far from showing that Kazakov ***necessarily*** and ***inevitably*** meets every limitation of the asserted claims, Dr. Fearon admits that the samples used by Kazakov "***may*** contain cell-free fetal DNA, since that is one of only two ***possible*** explanations it provides." Fear. Decl. ¶156 (emphasis added); *see also* Root Decl. Ex. 7 at 174:20-175:6 (stating that Kazakov *et al*. "leave open and state that possibility" in regard to the detection of cffDNA). But the alleged inherently disclosed element must be more than "probably" or "possibly" present; rather, it must be ***certainly*** present, and so recognized by persons of ordinary skill. *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). Dr. Fearon admitted the uncertainty of the Kazakov reference: "the authors obtained such findings but did not present them in the paper. If provided with a different translation[6] or more data, I might revise that interpretation." Root Decl. Ex. 7 at 138:18-139:2. Such equivocation is insufficient. *See Glaxo Inc. v. Novo-pharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995) (finding no inherency even though thirteen out of fifteen experiments produced the claimed crystals using the prior art method).

III. SEQUENOM HAS DEMONSTRATED IRREPARABLE HARM

Ariosa does not challenge in any meaningful way Sequenom's showing that irreparable harm is likely to occur absent injunctive relief. Ariosa tries to rebut Sequenom's showing by arguing that there is no evidence that any harm has occurred to date. Ariosa ignores the standard, which looks to the likelihood of future harm,[7] and three critical facts. First, Ariosa only recently launched its Harmony test: Ariosa did a "limited commercial launch" on March 26, 2012, and announced a "large-scale commercial launch" on May 7, just three weeks ago. Stuel. Decl. ¶ 9. Second, even with the limited release of the Harmony test, there is clear evidence that Sequenom is being harmed. Third, and most significantly, Ariosa soon will be offering and selling its Harmony test through its new partner, Laboratory Corp of America ("LabCorp"), the second largest clinical laboratory company in the United States. *Id.*

[6] Dr. Fearon was not able to vouch for the translation he was provided. Root Decl. Ex. 7 at 112:15-23.

[7] "[T]he injury need not have been inflicted when application [for a preliminary injunction] is made or be certain to occur; a strong threat of irreparable injury before trial is an adequate basis." Wright & Miller: Federal Prac. & Proc. s 2948.1, Grounds for Granting or Denying a Preliminary Injunction-Irreparable Harm (2012); *see also* Mot. at 12.

A. The Ariosa-LabCorp Deal Exponentially Increases The Likelihood That Sequenom Will Suffer Loss of Market Share, Goodwill And Reputation

Ariosa incorrectly argues that "there is simply no evidence of lost sales." Opp. at 22. There is already clear evidence of lost sales, even though Ariosa has so far conducted only a limited release of its Harmony test. Ariosa's launch, which began March 26, was limited to six hospitals, four of which have exclusive arrangements with Ariosa. Stuel. Decl. ¶ 9. [redacted] Welch Suppl. Decl. ¶¶ 5-9.

The harm to Sequenom likely will be exponentially greater when Ariosa implements "the large-scale, commercial launch of the Harmony test, in collaboration with our partner LabCorp" that Ariosa announced on May 7. Stuel. Decl. ¶ 9. Through its exclusive partnership with LabCorp, Ariosa will have a ready-made nationwide distribution network with LabCorp exclusively promoting the Harmony test at its over 1,700 patient service centers and to its well-established client base. Root Decl. Ex. 13 at 96:2-14. With the advent of Ariosa's exclusive relationship with LabCorp, Sequenom faces an even greater threat of irreparable harm (Welch Suppl. Decl. ¶¶ 11-16), and the propriety of injunctive relief is even more evident. *See Momenta Pharms., Inc. v. Amphastar Pharms., Inc.*, 2011 WL 5882184, *3-4 (D. Mass. Nov. 23, 2011) (refusing to dissolve or stay preliminary injunction, noting that competitor's sales following initial launch had "some effect" on the market, but "it is presumed that a ***full-blown launch*** of defendants' generic ***would have a substantially greater effect***") (emphasis added).

Knowing that its [redacted] arrangement with LabCorp bespeaks irreparable harm for Sequenom, Ariosa tried to hide it in discovery. Though highly relevant, Ariosa refused to produce the contract before the May 18 deposition of its chosen expert economist, Dr. Ryan Sullivan, on the ground that Dr. Sullivan did not review the contract and did not rely on it for his analysis. Root Decl. ¶¶ 25-26, Ex. 13 at 100:3-9. [redacted] *Id.* at 108:11-109:2. Still, Dr. Sullivan allowed that "data demonstrate that Ariosa could be much more successful in its sales even than Sequenom." *Id.* at 71:17-72:3.

Finally, after yet another request, Ariosa produced the contract ***during*** the deposition of its Executive Chairman, Dr. John Stuelpnagel, on May 23. Root Decl. ¶ 26, Ex. 1 at 100:25-101:5. Dr. Stuelpnagel testified [redacted] *Id.*, Ex. 1 at 181:24-182:11. Ariosa's strategy is to dominate the market with LabCorp. Dr. Stuelpnagel testified that "we are making the Harmony Test the most accessible test in the non-invasive prenatal diagnostic space through our relationship with LabCorp" (*Id.* at 50:18-21), and Ariosa's CEO, Dr. Song, wrote to LabCorp: "We should be able to dominate this market together." Root Decl. Ex. 14.[8]

Ariosa's argument is that "this large, available market" is big enough to accommodate its infringing test. Opp. at 22-23. Ariosa posits that the "available" market is ***all*** pregnant women, which assumes a fully-penetrated, mature market, and that the test is appropriate for use in the low-risk population. Root Decl. Ex. 1 at 62:7-15. In reality, the market is in the early stages and market demand is driven by Maternal Fetal Specialists (MFMs) and OB/GYNs, whom Sequenom is targeting for adoption of its MaterniT21 test. Welch Decl.¶¶ 16-21. Ariosa is targeting this very same market. Root Decl. Ex. 1 at 176:18-177:9 & Ex. 15 at pg. 18 (Ariosa "will draft on Sequenom's efforts to go after same geographies"). Sequenom likely will lose substantial market share, as it must compete with Ariosa's infringing test for the same early adopters in this nascent market that Sequenom began pioneering just seven months ago. Loss of market share in a nascent market constitutes irreparable harm. Mot. at 20-21. Ariosa ignores this critical point.

Further, Ariosa's entry into the market with its infringing test is likely to cause irreparable injury to Sequenom's reputation as a technology and market leader. *See id.* Ariosa ignores this point because Ariosa's strategy is to follow fast upon Sequenom's pioneering efforts and deprive Sequenom of its patent-protected technology leadership. Ariosa's Executive Chairman testified about Ariosa's "strategies of being a fast follower and letting your competitor educate the market around the

[8] Ariosa's marketing documents and internal communications tell a consistent story of its strategy of "crippling" Sequenom and "owning" the market. *See, e.g.*, Root Decl. Exs. 16-18. Ariosa's Chairman testified that as a result of the company's aggressive pricing strategy, "Sequenom would have a harder time to compete in the same market segment that we were competing with." Root Decl. Ex. 1 at 138:12-20.

advantages to cell-free DNA in the case of Sequenom and then being able to offer what we believe is a better test." Root Decl. Ex. 1 at 177:17-178:12. Irreparable injury occurs when, as here, an infringer deprives a patentee of "the recognition of being a technology innovator." *TruePosition Inc. v. Andrew Corp*., 568 F. Supp. 2d 500, 532 (D. Del. 2008). In addition, Ariosa's marketing to the low-risk population is contrary to FDA guidance and key opinion leaders in the field, and threatens to ruin this nascent market. Evans Suppl. Decl. ¶¶ 91-100.

B. Ariosa's Opposition Confirms The Likelihood Of Price Erosion

When Sequenom filed its moving papers, the available information indicated that Ariosa planned to offer its Harmony test at the list price of $900. Welch Decl. ¶ 47. Since then, Ariosa has publicly announced that the list price of the Harmony test is $795, which presents an even greater price differential to MaterniT21's list price of $2,762. Establishing reimbursement rates is a matter of negotiation with health insurance payors. Mot. at 15-18; Welch Decl. ¶¶ 30-35. [redacted] Welch Suppl. Decl. ¶ 17. This contract is not, as Ariosa argues, evidence that Sequenom will not suffer price erosion ***after*** full commercial launch of the Harmony test. The commercial availability of the Harmony test will inevitably weaken Sequenom's ability to negotiate favorable pricing. As Ariosa's expert agreed, payors will use the dramatically lower-priced Harmony test "to attain price concessions" from Sequenom. Root Decl. Ex. 13 at 186:23-187:6.

Ariosa's argument that the presence of another competitor, Verinata, lets Ariosa off the hook for price erosion (and lost sales) of the MaterntiT21 test is wrong as a matter of fact and law. Verinata has a considerably higher price ($1,200) for its test than Ariosa's $795 price, and Verinata has not been nearly as visible in the market as Ariosa. Welch Suppl. Decl. ¶ 18; Sull. Decl. ¶ 51. Ariosa's Executive Chairman testified that "Ariosa has significant competitive advantages over [Verinata]" and that Verinata does not have a distribution partner like LabCorp. Root Decl. Ex. 1 at 168:11-15; 169:11-14. "It is well-established that the 'fact that other infringers may be in the marketplace does not negate irreparable harm.'" *Robert Bosch LLC v. Pylon Mfg. Corp*, 659 F.3d 1142, 1151 (Fed Cir. 2011) ("Picking off one infringer at a time is not inconsistent with being irreparably harmed.").

C. Harm Sequenom's Ability To Raise Capital; Ariosa's Inability To Pay Damages

Ariosa does not challenge the analysis of Sequenom's expert economist, who concluded that Ariosa's entry into the marketplace would likely harm Sequenom's ability to raise capital in the near-term ***future***. Rao Decl. ¶¶ 39-45. Instead, Ariosa relies on testimony from a non-expert witness that Sequenom has never had difficulty raising capital in the ***past***. Opp. at 23. Past ability to raise capital is irrelevant; the question is whether Ariosa's entry will likely harm Sequenom's ability to raise capital, and Dr. Rao's unchallenged analysis shows that it will.

Another irreparable harm is that Ariosa likely would not have the financial ability to pay damages even if the harms were reparable. [redacted] Root Decl. Ex. 1 at 93:16-22. Ariosa's expert argues that allowing Ariosa to sell its infringing test will provide the funds to pay damages. Sull. Decl. ¶¶ 75-77. This argument is absurd. It ignores that Sequenom's rightful profit margin on the sale of a MaterniT21 test is hundreds of dollars higher than Ariosa's revenues on its Harmony test, so Ariosa's infringing sales would not generate enough to cover Sequenom's lost profits, let alone damages for price erosion, and treble damages for willful infringement.

IV. THE BALANCE OF HARDSHIP AND PUBLIC INTEREST FACTORS

The authorities cited in Sequenom's opening brief make clear that an infringer cannot complain if its business is destroyed by an injunction against continuing infringement. Mot. at 23-24. Ariosa incorrectly argues that this law does not apply in the preliminary injunction context. In that context, the Federal Circuit rejected a hardship claim of a generic challenger whose "harms were 'almost entirely preventable' and were the result of its own calculated risk to launch its product pre-judgment." *Sanofi-Synthelabo v. Apotex, Inc*., 470 F.3d 1368, 1383 (Fed. Cir. 2006). In contrast, absent injunctive relief, Sequenom will continue to suffer encroachment of its patent rights, loss of customers, injury to goodwill and reputation, and loss of market share. The public interest is best served by enforcing patent rights (*see id.*; Mot. at 24-25) and having all prenatal diagnostic tests appropriately tested and validated for the population to which they are made available. Evans Decl. ¶¶ 152-55. Ariosa's strategy to promote its Harmony test to populations without proper clinical studies and validation is most assuredly contrary to the public interest. *Id.*; Evans Supp. Decl. ¶¶ 91-100.

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Respectfully submitted,

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